The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Pazopanib
Study Number: VEG117365
Title: PGx6652: Genetic Evaluation of Pazopanib–Related Hepatotoxicity
Rationale: Pazopanib, an oral angiogenesis inhibitor, is approved for the treatment of advanced renal cell carcinoma (RCC) and soft tissue sarcoma (STS). Elevations in serum alanine aminotransferase (ALT) were observed in pazopanib clinical studies. Concurrent elevations of ALT and bilirubin without alkaline phosphatase elevation, conditions which may be associated with severe liver injury, were rare (~1%). Using both candidate gene and genome-wide approaches, this exploratory phamacogenetic (PGx) analysis evaluated associations between genetic variants and hepatotoxicity in pazopanib-treated subjects with cancer.
Study Period: 02 November, 2012 - 20 May, 2014
Objectives: To identify genetic variants associated with pazopanib-related hepatotoxicity
Indication: Cancer
Study Investigators/Centers: GSK conducted this pharmacogenetic experiment using DNA samples collected in the pazopanib clinical studies (see a list of studies in Data Source section).
Research Methods: Candidate genetic variants were tested for their association with concurrent ALT and bilirubin elevations using data from 16 pazopanib clinical studies (pazopanib monotherapy or combination therapy for cancer). Genome-wide association study (GWAS) and *HLA* analyses were performed to assess associations between genetic variants and ALT elevation using data from eight clinical studies (pazopanib monotherapy for RCC, STS or ovarian cancer). Data included in the analyses were derived from pazopanib-treated subjects who provided informed consent and a sample for PGx analysis in the clinical studies. DNA was extracted from venous blood using the Qiagen Autopure LS or QiAmp DNA Blood Kit (Qiagen Inc, Valencia, CA). For the candidate gene analysis of concurrent ALT and bilirubin elevations, most of the genotype data were generated previously (VEG115002, VEG116087, VEG116103, and VEG116747), and were re-used in this analysis. Where genotype data were not available from the previous studies, they were generated using the Affymetrix DMET Plus Array, GeneScan, and Sequence Based Typing by BioStorage Technologies (Piscataway, NJ), Gen-Probe (Manchester, UK), ShanghaiBio Corporation (Shanghai, China), Histogenetics (Ossining, NY), and Beijing Anapure (Beijing, China). For the meta-analysis of ALT elevation, GWAS data generated previously in VEG115002, VEG116087, VEG116103, and VEG116747 were re-used in this analysis. Imputation based on a reference panel of haplotypes from the 1000 Genomes project was conducted to generate a set of ~30 million genetic variants genome wide for statistical analysis. *HLA* genotyping was conducted by Histogenetics (Ossining, NY) and Beijing Anapure (Beijing, China). All the vendors who were involved in experimental data generation for GSK did so through a fee-for-service agreement.
Data Source: Clinical and genotype data from clinical studies VEG102616, VEG105192, VEG107769, VEG108844, VEG113078, VEG110727, VEG110655, VEG114012, VEG107200, VEG105427, VEG111109, VEG110264, VEG109607, VEG111128, HYT109091 and VEG20007 were used in the candidate gene analysis of concurrent ALT and bilirubin elevations. Clinical and genotyping data from clinical studies VEG102616, VEG105192, VEG107769, VEG108844, VEG113078, VEG110727, VEG110655, and VEG114012 were used in the GWAS and *HLA* analyses for ALT elevation.
Study Design: This was a retrospective, non-interventional pharmacogenetic investigation to identify germline genetic variants that are associated with pazopanib-related hepatotoxicity. In the PGx analysis of concurrent ALT and bilirubin elevations, associations between candidate genetic variants and case/control status were tested. The selected candidate genetic variants included *HLA* alleles and functional variants in genes involved in pazopanib metabolism and disposition. 'Cases' were subjects who had concurrent ALT (≥3xULN) and bilirubin (≥2xULN) elevations from 16 clinical studies (see Data Source section). 'Controls' were subjects selected from clinical studies VEG102616, VEG105192 and VEG107769 who a) received pazopanib (800mg/day) for at least 12 weeks, b) had both ALT and total bilirubin measurements within the on-therapy window that were all ≤ULN, and c) had matching race and ethnicity with cases. GWAS and *HLA* analyses for on-treatment ALT elevation were conducted using data from eight clinical studies (see Data

Source section). Endpoints analyzed were maximum ALT (within the on-therapy window) and time to event (event as first on-treatment ALT ≥3xULN or ≥5xULN).

Study Population: The PGx analysis populations consisted of subjects who provided written informed consent and a blood sample for genetics research and received at least one dose of pazopanib. In the candidate gene analysis of concurrent ALT and bilirubin elevations, there were 32 cases and 70 controls. In the GWAS and *HLA* analyses of ALT elevation, the number of subjects in each of the analyses is summarized in the table.

	Maximum ALT, N	3xULN event, N	5xULN event, N	Time to event, censored (ALT≤ULN), N
GWAS analysis	1225	248	142	512
HLA analysis	1228	252	145	509

Study Exposures, Outcomes: Pazopanib-treated subjects with cancer in the 16 or eight clinical studies.

Data Analysis Methods: In the candidate gene analysis of concurrent ALT and bilirubin elevations, logistic regression was used to assess the association of genotypes with case/control endpoint including self-declared race/ethnicity as a covariate. Ten genetic variants in six genes were tested, with $p \leq 0.005$ as the significance threshold after adjustment for the number of tests performed in this analysis.

In the GWAS and *HLA* analyses for ALT elevation, linear and Cox regressions were ultilized, respectively, to test the associations between genotypes and maximum ALT and time to event endpoints. GWAS meta-analysis included age, sex, baseline ALT and principal components (PCs) as covariates in the 'Full model', and the PCs as a covariate in the 'PC only' model. The conventional genome-wide significance threshold ($p \leq 5x10^{-8}$) was applied to assess GWAS significance for common variants (minor allele frequency ≥5%). *HLA* analysis using pooled data included age, sex, baseline ALT and self-declared race/ethnicity as covariates in the 'Full model', and self-declared race/ethnicity as a covariate in the 'PC only model'. Ninety-two *HLA* alleles had minor allele frequency ≥1% and were evaluated in this analysis with $p \leq 0.0005$ (0.05/92) as the significance threshold after adjustment for the number of *HLA* alleles tested.

Limitations: This genetic analysis was carried out using clinical data and DNA obtained during the conduct of the clinical trials. These clinical trials did not consider pharmacogenetic analysis in study designs; subject consent for participation to genetic research was optional. The available sample size in this genetic experiment limits the statistical power to allow identification of relatively large genetic effects. Consequently, failure to demonstrate an association between any particular genetic marker and the clinical endpoints could be due to lack of statistical power.

Study Results: Genetic variants in *UGT1A1* (*28, *37, and *6) were associated with incidence of concurrent ALT (≥3xULN) and bilirubin (≥2xULN) elevations in subjects treated with pazopanib [p=0.001, odds ratio =7.3 (95% CI 2.2-24.2), recessive genetic model]. In the GWAS analysis, a common genetic variant (rs80228453) near the *NNT* gene showed a genome-wide association with maximum ALT ($p=2x10^{-8}$) in the PC only model. No common genetic variants were associated with time to ALT elevation event endpoints in the Full or PC only analysis model at the genome-wide significance level ($p \leq 5x10^{-8}$). In the *HLA* analysis of ALT elevation, *HLA-B**57:01 was significantly associated with maximum ALT and time to 5xULN event in both the Full and PC only models after adjustment for the number of *HLA* alleles tested ($p \leq 0.0005$), with the strongest association being with time to 5xULN in the Full model (p=0.00009).

Conclusions: *UGT1A1* polymorphisms were associated with incidence of concurrent ALT and bilirubin elevations in subjects treated with pazopanib; this finding may be applied to characterize the risk of liver toxicity. A common genetic variant (rs80228453) near the *NNT* gene was associated with maximum ALT in pazopanib-treated subjects at genome-wide significance ($p \leq 5x10^{-8}$). *HLA-B**57:01 was significantly associated with ALT elevation after adjustment for the number of *HLA* alleles tested. Both the *NNT* and *HLA* associations need confirmation in an independent dataset.

Last updated: 20 May 2014